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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/776,180	02/12/2004	Marc Beauregard	15493-2US	3080

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EXAMINER	
LIU, SUE XU	
ART UNIT	**PAPER NUMBER**
1639	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/25/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/776,180	BEAUREGARD ET AL.	
	Examiner	Art Unit	
	Sue Liu	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,7 and 10-17* is/are pending in the application.

4a) Of the above claim(s) *11-17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 7, and 10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Withdrawal of Finality

1. Upon further consideration, the finality of the previous Office action (mailed 9/29/06) has been withdrawn due to new rejections that are not necessitated by applicant's amendment to the claims.

Claim Status

2. Claims 4-6, 8, and 9 have been canceled as filed on 6/16/06;

Claims 1-3, 7, and 10-17 are currently pending;

Claims 11-17 have been withdrawn as previously acknowledged;

Claims 1-3, 7, and 10 are being examined in this application.

Election/Restrictions

3. Applicant's election without traverse of Group I (Claims 1-10) in the reply filed on 10/27/2005 is as previously acknowledged.

Priority

4. This application claims priority to provisional application 60/446,518 filed on 2/12/2003.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the **first paragraph of 35 U.S.C. 112**:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Scope of Enablement Rejection

6. Claims 1-10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for 1-propanol used in PCR reaction with certain thermo polymerases ($Vent_r^{®}$) and DNA template (MB-1 His gene) to generate mutations in DNA with certain length in the presence of 1-propanol with certain concentration, does not reasonably provide enablement for Taq polymerase, all DNA template and propanol with concentrations beyond 8%. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. §112, first paragraph, have been described *In re Wands*, 8 USPQ2d 1400(1988). They are:

1. The breadth of the claims;
2. The nature of the invention;
3. The state of the prior art;
4. The predictability or lack thereof in the art
5. The level of skill in the art;
6. The amount of direction or guidance present;
7. The presence or absence of working examples;
8. The quantity of experimentation needed.

The breadth of the claims

The breadth of the claims seems to encompass all polymerization reactions using any DNA template (with any length), and Taq (Thermus aquaticus DNA polymerase) or $Vent_r^{®}$ (Thermococcus litoralis DNA polymerase mutant) in the presence of 1-propanol with a concentration of between 0.1%-15%. The method further requires that the generated mutant nucleic acid encode for a "biologically active protein".

The nature of the invention

The nature of the invention is a method of generating mutations in PCR products (DNA fragments) by adding propanol to the polymerization reaction mixture.

The state of the prior art/ The predictablility or lack thereof in the art

The use of 1-propanol in PCR reaction with Taq polymerase would inhibit the polymerization reaction, as evidenced by applicant's own publication. Claveau et al (DNA and Cell Biology. Vol. 23 (11): 789-795; 2004), state the followings:

"Considering the deletion-to-mutation ratio and the low mutation frequency obtained with Taq in the presence of critical propanol concentration, we did not further investigate this condition, considering it unsuitable for error-prone PCR". (emphasis added; p. 791, right col., para 3).

This passage in the reference indicates that Taq polymerase cannot be used for the claimed method of generating mutations with polymerization reaction in the presence of 1-propanol.

In the same reference, applicants further state the followings:

"...the enzyme was able to amplify amplicons of 2.8kb. With 8.0% propanol, the longest amplicon obtained was 0.8kb." (p. 793, left col., para 1).

This passage in the reference indicates that the method can only be used to generate products that are no longer than 0.8kb with 8.0% propanol. This also indicates that it is highly unpredictable to use the claimed method to generate DNA fragments with any length.

In the same reference, applicants further state the followings:

"...increasing its concentration above 8% resulted in complete inhibition, indicating that the concentration range providing optimal error-prone PCR conditions is narrow." (p. 793, left col., para 1).

This passage in the reference indicates that only a "narrow" range of concentration of propanol will work with the claimed method. The claimed range of 0.1%-15% as recited in Claim 1 is beyond the critical 8%.

Furthermore, the reference states the following:

"increasing mutation rate to 10^{-1} error/bp/PCR or above... results in mutant libraries where no active genes are left" (emphasis added; p. 789, right col., right col.).

This passage in the reference indicates that certain mutant nucleic acid sequences cannot be "biologically active protein" as it is claimed in Claim 7 of the instant application. Thus, it is highly unpredictable whether a given mutant nucleic acid will encode for a "biologically active protein".

The level of one of ordinary skill

The level of skill would be high, and most likely at the Ph.D. level..

The amount of direction or guidance present/The presence or absence of working examples

The only guidance presented in the instant specification is directed to PCR amplification reactions using certain percentage of 1-propanol and Taq, or Vent polymerase (p. 17+ of the spec.). The specification does not recite methods of using Taq polymerases with any 1-propanol concentrations that are between 0.1-15%. Since concentrations of the alcohols used in the PCR reaction mix is important to the success of the method, and the experimentally determined critical alcohol concentration is unpredictable, detailed guidance should be provided for all the species claimed in the entire genus of alcohol. In addition, the instant specification also does not provide guidance of generating nucleic acids with any length.

The quantity of experimentation needed

Due to the unpredictabilities of the effects of various alcohol on different polymerases under different reaction conditions (as discussed supra), and the lack of guidance in the instant specification, large quantities of experimentation would be required. The art has demonstrated that 1-propanol would the reaction with Taq polymerase as discussed supra. In addition, to achieve mutations, certain alcohol concentrations must be used. Alcohol concentrations that are outside the critical range would inhibit the reaction, as discussed above. These concentration requirements appear to be not predictable and must be determined by experimentations. Since the instant specification only provides guidance for one example of (using propanol with Vent polymerase), undue experimentations must be carried out to practice the entire genus of claimed method.

Conclusion

Due to the large quantity of experimentation necessary to determine each specific reaction condition for each one of the combination of an alcohol and a polymerase as well as a specific reaction buffer and/or reagent; the lack of direction/guidance presented in the specification regarding the specific requirements for reaction conditions; the predictability of the effects of various alcohol on different polymerization reactions as established by the state of the prior art; the breadth of the claims to establish any structural or functional limitations, undue experimentations would be required of a skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

(Note: the instant claim numbers are in bold font.)

8. Claims 1-3, 7 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chevet et al (Nucleic Acids Research. Vol. 23(16): 3343-3344. 1995), and Buchi (Buchi, J. "The Constitution-Effect Relationships from a New Viewpoint" Deutsche Apotheker-Zeitung 1966, pages 1695-1700 (1-29 for English translation)).

The instant claims recite a method for inducing a random mutation into a nucleic acid sequence comprising the steps of:

Providing a nucleic acid sequence for use as DNA template:

Submitting said DNA template to polymerization reaction with at least one DNA polymerase selected from the group consisting of a *Thermus aquaticus* DNA polymerase and a *Thermococcus litoralis* DNA polymerase mutant, in presence of 1-propanol in a concentration of between 0.1% to 15%.

Chevet et al, throughout the reference, teach methods adding various reagents to PCR reactions. The reference teaches using Vent polymerase (p. 3344, right col., para 2), DNA as template (p. 3343), and ethanol (p. 3344, right col., para 2), which reads on the method of **clms 1 and 3**. The reference also teaches dNTP was used for the PCR reaction, which reads on the different nucleotides of **clm 10**. The reference also teaches the amplified DNA is encoding a surface protein (p. 3343, left col., para 2), which reads on **clm 7**.

Although the Chevet reference does not explicitly teach the reaction will induce random mutations as recited in the preamble of **clm 1**, in **clm 2, 7, and 10**, the "random mutation" is an inherent property of the Vent polymerase to induce random mutations including transversion/transition, as evidenced by Keohavong et al (PCR Methods and Applications, Vol 2, 288-292; 1993). Thus, the method using Vent polymerase would inherently produce random mutations as recited in **clms 1, 2, 7 and 10**.

The Chevet reference also does not explicitly teach the reaction is carried out in the presence of propanol.

However, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to substitute propanol (which has one more methylene group than ethanol) for ethanol to produce a homologous reaction mixture for PCR with favorable physicochemical properties (e.g., see MPEP §2144.09 "An obviousness rejection based on

similarity in chemical structure and function entails the motivation of one skilled in the art to make a claimed compound, in the expectation that compound similar in structure will have similar properties." In re Payne, 606 F.2d 303, 313, 203 USPQ 245, 254 (CCPA 1979). See In re Papesch, 315 F.2d 381, 137 USPQ 43 (CCPA 1963) (discussed in more detail below) and In re Dillon, 919 F.2d 688, 16 USPQ2d 1897 (Fed. Cir. 1991). Here, Buchi indicates that homologous compounds will lead to "optimal" properties (e.g., see Buchi, section 4.4.3, "the study of homologous series is extremely important for the development of medicines with optimal properties ... lengthening the alkyl groups causes modification of important physical and chemical properties and chemical reactivity with the receptor, resulting in a gradual change in the activity and type of effect"). Thus, the "optimal" properties exhibited with the ethanol homolog, propanol can improve the PCR reaction through various physico-chemical interactions.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sue Liu whose telephone number is 571-272-5539. The examiner can normally be reached on M-F 9am-3pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Doug Schultz can be reached at 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SL
Art Unit 1639
1/17/06

JON EPPERSON
PRIMARY EXAMINER